

PATENT SPECIFICATION

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(54) PARENTERAL BENZODIAZEPINE COMPOSITIONS

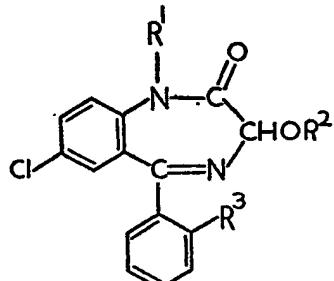
(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685 Third Avenue, New York 10017, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

The invention relates to pharmaceutical preparations containing benzodiazepins and in particular 5 - monocyclic aryl - 1,3-dihydro - 2H - 1,4 - benzodiazepine - 2 - one compounds which bear an oxygen containing substituent at the 3-position.

The 5 - monocyclic aryl - 1,3 - dihydro - 2H - 1,4 - benzodiazepin - 2 - one compounds which bear an oxygen containing substituent at position-3 of the benzodiazepine nucleus comprise an important class of medicinal agents which are useful, inter alia, as tranquillisers, anticonvulsants, and anti-anxiety agents. Typical of this class of compounds are 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepine - 2 - one, also known as oxazepam, and 7 - chloro - 5 - (o - chlorophenyl) - 1,3-dihydro - 3 - hydroxy - 2H - 1,4 - benzodiazepine - 2 - one, also called lorazepam and very many other, as shown in U.S. Patent 3,296,249. Although these compounds are orally active, a need exists for parenteral solutions of these drugs for use where oral administration is not feasible or desirable, such as in the case of an unconscious person, or one seriously disturbed, or where rapid onset of action is desired. Unfortunately, however, these 3 - oxygenated 1,4 - benzodiazepin - 2 - ones do not lend themselves to incorporation into the common parenteral formulations, e.g., aqueous solutions. The subject chemical compounds are themselves highly water insoluble. Further, they are so weakly basic that they do not form water soluble salts with pharmaceutically acceptable acids suitable for parenteral administration.

As a result, the formulation of satisfactory parenteral preparations, which are physiologically acceptable, contain a sufficient concentration of drug to be medicinally useful, and possess sufficient chemical stability, has presented a continuing problem. U.S. Patents 3,123,529 and 3,228,834 describe partially aqueous parenteral formulations for the benzodiazepine drugs diazepam and chlordiazepoxide respectively (neither of which bears an oxygen containing substituent at position-3 of the benzodiazepine nucleus). Formulations of these types are not suitable for the commercial preparation of parenteral solutions of the benzodiazepine compounds to which the present invention relates. A formula of the type described in Patent No. 3,123,529 provides solutions of the subject benzodiazepines which are highly unstable; the 3,228,834 formula on the other hand describes a diluent which is mixed with the benzodiazepine compound only shortly before administration. The present invention, however, provides non-aqueous parenteral solutions which are generally quite stable on storage, may be administered directly, are physiologically acceptable, and contain medically useful amounts of drug.

According to the invention there is provided a parenterally acceptable composition comprising from 10% to 65% polyethylene glycol, from 35% to 90% propylene glycol, from 0% to 10% benzyl alcohol, and, per ml. of the above solution from 1 mg. to 15 mg. of a benzodiazepine compound of the formula:



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wherein R¹ and R² are independently hydrogen or methyl and R³ is hydrogen or chlorine.

The compositions of the invention are clear solutions suitable for parenteral injection. They are chemically quite stable on storage, (usually highly stable) and thus provide a dosage form which may be maintained in read-to-use form, thus making unnecessary such undesirable operations as separate packaging of diluent and drug, or the need for reconstitution shortly before administration.

The formulations of the present invention may be readily prepared by simple admixing of the described constituents. Thus one simply mixes together the desired amounts of polyethylene glycol and propylene glycol within the scope of the invention, and adds thereto the required amount of the benzodiazepine compound, with stirring to achieve solution. If sterile materials are used, and sterile conditions are maintained, following filtration the resulting material is suitable for parenteral use with no further processing. Alternatively, the solution may be sterilised by procedures known in the art, such as bacteriological filtration. In either case, the solution is packaged under sterile conditions to provide a stable parenteral dosage form capable of undergoing storage for long periods of time with no significant deterioration.

The mixing of ingredients is conveniently performed at room temperature. Depending on the particular formulation and benzodiazepine compound used, however, it is sometimes desirable to dissolve the drug in the glycol mixture at slightly elevated temperature, as for example 55-60°, to promote dissolution.

Wherever percentages are given in this specification and in the claims, they represent percentages by volume and are based on the total volume of the solvent composition.

Although it is not essential to practice of the invention, in a preferred embodiment benzyl alcohol at a concentration of up to 10% may be incorporated in the composition. The benzyl alcohol has the desirable properties of exerting an anti-bacterial action and also of providing an anaesthetic effect upon parenteral administration of the drug. Additionally, if desired, other substances such as bactericides may be added.

In addition to being useful for direct parenteral administration, the solutions of the invention are also compatible with physiological solutions such as water for injection, 5% dextrose in water, and physiological saline, and may be administered in admixture with such injection solutions.

The particular dosages of the compositions of the invention to be employed in therapy should be individualised, and will vary according to the particular condition being treated, the route of administration, the size and species of the animal being treated, and the

particular benzodiazepine compound being administered. The determination of the particular dosage is well within the skill of the attending physician. Generally, a dosage which supplies from 1 to 75 mg. of drug is employed, and preferably from 5 to 50 mg., either intravenously or intramuscularly.

The following examples, which are not meant to be limitative, will further illustrate the practice of the invention.

Example I

18 ml. polyethylene glycol is mixed with stirring with 75 ml. propylene glycol and 2 ml. benzyl alcohol. To this solution is added 1.5 g. of 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 3 - hydroxy - 2H-1,4 - benzodiazepine - 2 - one followed by the addition of sufficient propylene glycol to provide 100 ml. solution. The mixture is stirred at room temperature to obtain a clear solution containing 15 mg/ml drug.

Storage of the above solution at refrigerator temperature for 37 months showed satisfactory chemical and physical stability.

Example II

In a similar manner to that of Example I, stable solutions containing 5 mg/ml drug are prepared by substituting for the benzodiazepine compound of Example I. 0.5 g. of either 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one or 7 - chloro - 1,3 - dihydro - 3 - hydroxy - 1 - methyl - 5 - phenyl - 2H - 1,4 - benzodiazepin - 2 - one.

Example III

20 ml. polyethylene glycol is admixed with 75 ml. propylene glycol. To this solution is added 1.0 g. of 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 3-hydroxy - 2H-1,4 - benzodiazepin - 2 - one, with stirring, followed by the addition of sufficient propylene glycol to provide 100 ml. total volume, to yield a clear stable solution containing 10 mg. drug per ml.

Example IV

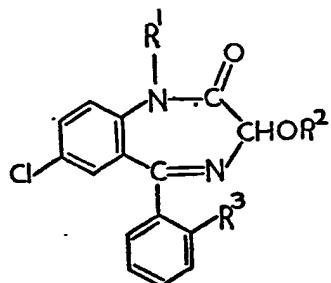
50 ml. polyethylene glycol is mixed with 45 ml. propylene glycol. The glycol mixture is heated to 55°C., and there is added, with stirring, 0.5 g. of 7 - chloro - 5 - (o - chlorophenyl) - 1,3 - dihydro - 1- methyl - 3-methoxy - 2H - 1,4 - benzodiazepin - 2 - one. A clear solution is obtained, which remains so upon cooling to room temperature or below. Sufficient propylene glycol is added to provide a total volume of 100 ml.

This solution, containing 5 mg. drug per ml. was stored for 24 months at room temperature with no losses being observed.

In the above examples we have found it convenient to employ polyethylene glycol having an average molecular weight 300 or

400. In general it is preferred that the poly-
ethylene glycol used in the compositions of
this invention is liquid at room temperatures,
however, solid polyethylene glycols may be
5 employed.

(WHAT WE CLAIM IS:—
1. A parenterally acceptable composition
comprising from 10% to 65% polyethylene
glycol, from 35% to 90% propylene glycol,
10 from 0% to 10% benzyl alcohol and, per
ml. of the above solution, from 1 mg. to
15 mg. of a benzodiazepine compound of the
formula



wherein R¹ and R² are independently hydro-
gen or methyl, and R³ is hydrogen or
chlorine.

2. A composition according to Claim 1
wherein R¹ and R² are hydrogen, and R³
is chlorine.

3. A composition according to Claim 1
wherein R¹ is methyl, R² is methyl, and R³
is chlorine.

4. A composition according to any one of
Claims 1 to 3 wherein the polyethylene glycol
concentration is about 18%, the propylene
glycol concentration is about 80%, and the
benzyl alcohol concentration is about 2%.

5. A composition according to any one of
Claims 1 to 3 wherein the polyethylene glycol
concentration is about 20%, and the propylene
glycol concentration is about 80%.

6. A composition according to any one of
Claims 1 to 3 wherein the polyethylene glycol
concentration is about 50% and the propylene
glycol concentration is about 50%.

7. A parenterally acceptable composition
substantially as hereinbefore described with
reference to any one of the specific Examples.

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